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THE NEUROBIOLOGICAL TOLL OF CHILD ABUSE AND NEGLECT

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Exposure to interpersonal violence or abuse affects the physical and emotional well-being of affected individuals. In particular, exposure to trauma during development increases the risk of psychiatric and other medical disorders beyond the risks associated with adult violence exposure. Alterations in the hypothalamic-pituitary-adrenal (HPA) axis, a major mediating pathway of the stress response, contribute to the long-standing effects of early life trauma. Although early life trauma elevates the risk of psychiatric and medical disease, not all exposed individuals demonstrate altered HPA axis physiology, suggesting that genetic variation influences the consequences of trauma exposure. In addition, the effects of abuse may extend beyond the immediate victim into subsequent generations as a consequence of epigenetic effects transmitted directly to offspring and/or behavioral changes in affected individuals. Recognition of the biological consequences and transgenerational impact of violence and abuse has critical importance for both disease research and public health policy.

Key words: *stress; corticotrophin releasing factor; development; cortisol; abuse*

Violence against women takes a profound toll on the mental health of the immediate victims and increases the risk of mental illness in future generations. Abuse early in life has unusually robust and sustained effects. Childhood physical or sexual abuse is associated with adult health problems including somatic symptoms, psychological problems, and substance abuse; for many variables, this association is as strong as for patients experiencing current abuse (McCauley et al., 1997). In addition, women with a history of sexual abuse

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display onset of depression earlier in life and appear to engage in more harmful and self-defeating coping strategies (Gladstone et al., 2004). Furthermore, a powerful graded relationship exists between adverse childhood experiences and risk of attempted suicide throughout the life span (Dube et al., 2001). Individuals who experience stress early in life have been hypothesized to develop pathophysiological changes in the central nervous system (CNS) that increase their vulnerability to stress later in life, predisposing them to mental and physical disorders. Because not every child exposed to abuse goes on to develop adult disease, it is possible that individuals who fall ill possess a preexisting genetic vulnerability that interacts with early adverse experiences, increasing the risk of developing stress-related pathology.

The potent and robust effects of early life abuse on lifelong mental and physical health have led to neurobiological theories of potential mechanisms underlying these adverse effects. The stress diathesis model posits that excess reactivity of certain neural and endocrine systems increases individual vulnerability to stress-related disease. Exposure to stress during developmentally critical periods results in persisting hyperreactivity of the physiological response to stress, increasing the risk of stress-related disease in genetically susceptible individuals (Figure 1). This article reviews the effects of stressful early life events on the hypothalamic-pituitary-adrenal (HPA) axis, the corticotropin-releasing factor (CRF) system, the subsequent development of mood and anxiety disorders in adulthood, and the potential for transgenerational effects. Data derived from both preclinical animal models and clinical research are summarized to comprehensively describe the neurobiological consequences of early life adverse events.

FIGURE 1: A schematic representation of the basic physiology of the hypothalamic pituitary adrenal (HPA) axis. When a stress response occurs, corticotrophin releasing factor (CRF) is excreted by the paraventricular nucleus of the hypothalamus (PVN). The release of CRF from the PVN stimulates the release of adrenocortiotropic hormone (ACTH) from the anterior pituitary. When ACTH binds to receptors in the adrenal medulla, glucocorticoids are released into the circulation. Glucocorticoids, cortisol in primates and corticosterone in rodents, bind to receptors in the hippocampus, PVN, and pituitary to modulate the continuance or cessation of the response as well as adaptation. Exposure to chronic stressors, particularly during development, leads to modifications in receptor systems in the HPA axis and thereby hypo- or hyperactive stress responses. Because glucocorticoids also modulate metabolism and immune function, chronic stimulation of the HPA axis can have profound effects on the entire body.

PATHOBIOLOGY OF THE STRESS RESPONSE: THE CRITICAL ROLE OF CRF

To understand the basis of long-term biological changes that frequently follow exposure to violence and abuse, the biological events that occur in response to stress must first be reviewed. The chain of events in the body that is commonly referred to as the ''fight or flight response'' originally evolved to allow an organism to respond to a situation in which their life was being threatened. The body's response mobilizes energy for either a ''fight'' or a ''flight,'' thus the common name for the response. Both the nervous system and the endocrine system work in combination to direct all available resources to the task of overcoming the threatening stimulus (stressor).

The stress response occurs in two phases. Immediately upon detection of the stressor, in the first phase of the stress response, norepinephrine is released from nerve terminals of the sympathetic nervous system and epinephrine is released from the adrenal medulla into the general circulation (see Figure 1). Moments later, CRF is released by parvocellular neurons of the hypothalamic paraventricular nucleus into the hypothalamo-hypophyseal portal system for transport to the anterior pituitary gland where it stimulates the release of adrenocorticotropic hormone (ACTH) into the general circulation (Swanson, Sawchenko, Rivier, & Vale, 1983). ACTH is then humorally transported to the adrenal cortex where it stimulates the release of glucocorticoids (cortisol in primates and corticosterone in rodents) from the adrenal cortex. This chain of events that characterizes the HPA axis response typically takes several minutes to fully engage and represents the second phase of the stress response. Activation of the HPA axis is eventually reduced through negative feedback via stimulation of glucocorticoid receptors within the hippocampus, hypothalamus, and anterior pituitary (Jacobson & Sapolsky, 1991). In the short term, the stress response is extremely adaptive because it shifts biological resources toward physiological functions that promote escape and survival. However, if the stress response becomes chronic due to repeated exposure to stressors, defects at different levels of the negative feedback system, or both, the result is a sustained increase in the level of stress hormones and the initiation of pathological changes across multiple physiological systems, resulting in stress-related diseases (McEwen, 2008).

A great deal of research has focused on the preeminent role of CRF in the adaptive response to stress and the etiology of stress-related disease. Complimenting its major role in the regulation of the HPA axis and the endocrine response to stress, CRF also plays a key role in the extra-endocrine CNS response. CRF is broadly distributed in areas of the brain outside the hypothalamus including the monoaminergic brain stem nuclei, central nucleus of the amygdala, septum, bed nucleus of the stria terminalis, hippocampus, and the cerebral cortex (Swanson et al., 1983) where it functions as a neurotransmitter in coordinating the behavioral, autonomic, and immune responses to stress (Arborelius, Owens, Plotsky, & Nemeroff, 1999). Two G protein-linked subtypes of CRF receptors, CRF_1 and CRF_2, have been described (Chalmers, Lovenberg, Grigoriadis, Behan, & De Souza, 1996; Steckler & Holsboer, 1999). A high density of CRF_1 receptors is located in the anterior pituitary gland, as well as in a variety of subcortical and cortical brain regions. The CRF_2 receptors are predominantly expressed in the heart and some brain regions (i.e., septum, ventromedial hypothalamus, dorsal raphe nuclei). Stress responses appear to be mediated through the CRF_1 receptor, whereas the CRF_2 receptor may diminish stress responses (Arborelius et al., 1999). Of note, a recent report (Rees, Akbari, Steiner, & Fleming, 2008) indicates that stress during development increases CRF_1 receptor expression in the paraventricular nucleus of the hypothalamus.

Preclinical research suggests that increases in CRF release are necessary and sufficient for stress-related changes in affective behavior. Increases in depressive-like and anxious behaviors are observed following direct CNS CRF administration, including diminished food intake, disturbed sleep patterns, facilitation of fear conditioning, and decreased reproductive behavior (Dunn & Berridge, 1990; Owens & Nemeroff, 1991). In addition, direct CNS administration of CRF in nonhuman primates produces depressive symptoms, such as inactivity and huddling behavior (Kalin, Shelton, Kraemer, & McKinney, 1983). In laboratory experiments, administration of CRF also leads to fear conditioning, an enhanced startle response, and other anxiogenic behaviors (Dunn & Berridge, 1990). Agents that antagonize the effects of CRF have been found to attenuate the anxiety and depressive symptoms mediated by CNS administration of CRF (Dunn & Berridge, 1990; Skutella et al., 1994).

Consistent with preclinical findings, clinical studies have elucidated a variety of changes in CRF neurotransmission in patients who have been diagnosed with stress-related psychiatric illnesses, such as depression and posttraumatic stress disorder (PTSD). Elevated cerebrospinal fluid (CSF) CRF concentrations

have been documented in combat veterans with PTSD (Baker et al., 1999; Bremner et al., 1997) as well as depressed patients (Nemeroff et al., 1984; Wong et al., 2000), and increased numbers of CRF immunoreactive neurons and CRF messenger RNA (mRNA) expression have been observed in the postmortem tissue of depressed patients (Purba et al., 1995; Raadsheer, Hoogendijk, Stam, Tilders, & Swaab, 1994). In addition, postmortem studies of individuals who have committed suicide identified increased concentrations of CSF CRF (Arato, Banki, Bissette, & Nemeroff, 1989), decreased expression of CRF_1 receptor mRNA within the frontal cortex (Merali et al., 2004), increased CRF concentrations, and decreased density of CRF receptors within the frontal cortex in comparison to controls (Merali et al., 2004; Nemeroff, Owens, Bissette, Andorn, & Stanley, 1988). Finally, effective treatment of depression using either the antidepressants, fluoxetine or amitriptyline (De Bellis, Gold, Geracioti, Listwak, & Kling, 1993; Heuser et al., 1998), or the electroconvulsive therapy (ECT; Nemeroff, Bissette, Akil, & Fink, 1991) is associated with a reduction in pretreatment levels of CSF CRF concentrations.

As a consequence of the extensive preclinical and clinical findings linking hyperactivity of CRF neurotransmission with mood and anxiety orders, antagonists of the CRF_1 receptor are currently being evaluated for drug development as novel anxiolytics or antidepressants (Habib et al., 2000; Holsboer & Ising, 2008; Ising & Holsboer, 2007; Zobel et al., 2000). The results of one open study with R121919 were promising (Zobel et al., 2000). Although a recent clinical trial in major depression with a Pfizer compound was unsuccessful, this trial did not distinguish between individuals with and without exposure to early life stress (ELS; Binneman et al., 2008), and moreover the magnitude of CRF_1 receptor occupancy obtained in this study was unclear. Other CRF_1 receptor antagonist studies are ongoing. As discussed in detail in this review, individuals exposed to ELS may manifest a distinct endophenotype of depression characterized by marked hyperactivity of the CRF system. CRF_1 receptor antagonists may be particularly effective in this subset of patients.

In summary, CRF is a key mediator of the mammalian stress response. Dysregulation of the CRF system may explain the symptomatology of increased vigilance and enhanced startle observed in patients with anxiety disorders, such as PTSD, and may in part explain the high incidence of comorbid mood and anxiety disorders. Given the pivotal role of CRF in the response to stress, it may be a key mediator of stress-evoked pathologies including those which follow violence and abuse. To fully appreciate the consequences of early life abuse, it is also important to review the evidence for long-term and pleiotropic effects of abuse during development, effects which are likely mediated by changes in the HPA axis and CRF neurotransmission.

LONG-TERM CONSEQUENCES OF EARLY LIFE STRESS EXPOSURE

The preponderance of clinical data illustrates the long-term adverse impact of physical and sexual abuse on mental health. A large study of adult female twins demonstrated that childhood sexual abuse was associated with an increased risk of major depression. In addition, women with a history of sexual abuse were more likely to manifest depressive-like behaviors after stressful life events than women without a history of abuse (Kendler, Kuhn, & Prescott, 2004). The developmental timing of the abuse may also contribute to the clinical outcome of exposure to childhood trauma. Women abused prior to 13 years are equally likely to develop either PTSD or major depressive disorder (MDD); however, women abused after 13 years are more likely to develop PTSD than MDD (Maercker, Michael, Fehm, Becker, & Margraf, 2004). This divergence in clinical course may, in part, be linked to the development of the HPA axis and stress-coping mechanisms.

PERVASIVE AND ENDURING EFFECTS OF EARLY LIFE STRESS

- Neurodevelopmental Delays
- HPA Axis Dysfunction
- Metabolic Syndrome
- Cardiovascular Disease
- Immune System Dysfunction
- Major Depressive Disorder
- Post Traumatic Stress Disorder
- Compromised Reproductive Health
- Transgenerational Effects

Dysregulation of the HPA axis has been repeatedly documented following early life stress (ELS) and has been proposed as a potential mediator of the long-term effects of abuse. Much of the available information about the effects of early life sexual or physical abuse on mental and physical health come from the use of the Trier Social Stress Test (TSST), a well-validated method for assessing stress reactivity (Heim et al., 2000). During the TSST, the participant is asked to deliver a 10-min public address and performs a mental arithmetic task in the presence of a panel of evaluators. Variables measured include heart rate, plasma ACTH, and cortisol concentration at several intervals before, during, and after the performance component of the test. Heim and colleagues (2000) compared four groups of women: women without psychiatric illness or history of ELS serving as a control group (CON), depressed women without a history of ELS (non-ELS/MDD), depressed women with a history of ELS (ELS/MDD), and nondepressed women with a history of ELS (ELS/non-MDD). The greatest ACTH and cortisol responses and increases in heart rate in the TSST occurred in the ELS/MDD group. In fact, the ACTH response of these women was more than six times greater than that observed in the CON, indicative of marked hyperreactivity of the HPA Axis. These women exhibited greater rates of comorbid PTSD (85%) in comparison to the other groups. The increased reactivity of the HPA axis suggests that ELS produces an enduring sensitization of the HPA axis. In addition, the increased heart rate response to the TSST suggests a sensitization of the autonomic nervous system. The profound effects of ELS on the reactivity of these two systems may constitute an important etiological element in the development of stress-related adult psychiatric disorders, including major depression and PTSD.

To further explore the hypothesis that ELS alters set points of the HPA axis, standard HPA axis challenge tests (CRF stimulation test and $ACTH_{1-24}$ stimulation test) were performed in a similar population of women (Heim, Newport, Bonsall, Miller, Nemeroff, 2001). Depressed women, irrespective of history of abuse, exhibited a blunted ACTH response to exogenously administered CRF. In contrast, women who were not currently depressed, but reported a history of abuse, had an exaggerated ACTH response following CRF infusion as compared to nondepressed, nonabused women. These same abused, nondepressed women had lower plasma cortisol concentrations at baseline and after administration of $ACTH_{1-24}$. Similar effects of ELS have also been reported for female participants using the dexamethasone/CRF test (Tyrka et al., 2008). Collectively, these findings provide a robust demonstration of prolonged consequences of early life abuse on the HPA axis of women, both with and without current MDD. The HPA axis is not the only neuroendocrine system altered by ELS; recently, CSF concentrations of oxytocin, a neuropeptide of paramount importance in a variety of female reproductive behaviors including maternal behaviors, childbirth, and breast-feeding, have been shown to be markedly reduced in adult women who were victims of child abuse (Heim et al., 2008).

In addition to the neuroendocrine and neurotransmitter alterations observed in patients with ELS, there is evidence that such experiences may also alter brain structure. The hippocampus is a prominent substrate for glucocorticoid-mediated negative feedback on HPA axis activity. In addition, this area is particularly sensitive to stress-induced damage, likely due to the colocalization of glucocorticoid receptors and glutamate receptors. Glucocorticoids inhibit glucose uptake into hippocampal neurons and augment damage (Armanini et al., 1990), as illustrated by the finding that stress-induced elevations in glucocorticoid concentrations exacerbate neuron loss in the hippocampus (Stein-Behrens et al., 1994). Cell death has been demonstrated following severe chronic stress (Uno et al., 1989), and in less severe cases, stress-induced alterations in dendritic morphology and neurotransmitter receptors have been documented (McEwen, 1994; Sapolsky, 2003). In addition, changes in hippocampal cytoarchitecture after chronic stress have been associated with changes in mood as well as cognition (McEwen & Magarinos, 2001).

Clinical brain imaging studies of the hippocampus reinforce these preclinical findings.

Reduced hippocampal volume is found in some, but not all, patients with unipolar depression (Campbell & Macqueen, 2004). In addition, hippocampal atrophy is greatest in depressed patients with a higher total lifetime duration of depression (Sheline, Sanghavi, Mintun, & Gado, 1999; Sheline, Wang, Gado, Csernansky, & Vannier, 1996;). ELS has also been linked to decreased hippocampal volume (Driessen et al., 2000; Stein, Koverola, Hanna, Torchia, & McClarty, 1997); and ELS may be an important contributor to reduced hippocampal volume in depression. To evaluate this hypothesis, hippocampal volume was measured in depressed women with and without a history of ELS, as well as in a CON of women. Reduced hippocampal volume was found to occur solely in depressed women with a history of ELS. Depressed women without ELS and women from the CON had similar hippocampal volumes (Vythilingam et al., 2002). These data suggest that previous reports of reduced hippocampal size in patients with depression may in fact be more related to a history of ELS rather than to depression per se. The implications of reduced hippocampal volume are not fully understood but likely include dysregulation of the HPA axis and cognitive impairment. The concatenation of findings demonstrates that ELS alters the HPA axis and markedly increases the risk of depression and other disorders.

Because of the limitations associated with conducting experiments in human participants, animal models are invaluable in understanding the pathologic consequences of stress and trauma exposure. A multitude of preclinical studies have demonstrated that early life stressful experiences, such as maternal deprivation, exert both acute and long-term effects on neuroendocrine, cognitive, and behavioral systems (Gutman & Nemeroff, 2002). Early stress appears to produce persistent changes in CRF-containing neural circuits, increasing the risk of development of mood and anxiety disorders in adulthood. Research using rodent and nonhuman primate models of ELS has provided significant insight into the consequences of ELS on the biology of the HPA axis. These data suggest that the abnormalities of HPA activity described in depressed patients with ELS are a direct consequence of stressful experiences during development (Heim, Plotsky, & Nemeroff, 2004). Laboratory animals exposed to stressful conditions during development manifest adverse short- and long-term cognitive dysfunction and abnormal behavior associated with alterations of the normal physiology and genetic regulation of the CRF system (Gutman & Nemeroff, 2003; Ladd et al., 2000). Pathological stress responsiveness in adult mammals appears to be mediated in part through the effects of developmental stress on the neural systems mediating the expression of fear (Caldji et al., 1998; Caldji, Francis, Sharma, Plotsky, & Meaney, 2000; Liu et al., 1997) and the quality of maternal care early in development may be a moderating influence that has substantial effects on the ontogeny of the stress response in adult animals (Szyf, Weaver, Champagne, Diorio, & Meaney, 2005).

The consequences of social deprivation or impaired maternal care as a form of ELS have been studied extensively using a variety of nonhuman primate models (Suomi, 1991, 1997). Social deprivation models in which infant monkeys are raised in isolation from their mother result in depressive symptoms and reduced CSF norepinephrine concentrations (Kraemer, Ebert, Schmidt, & McKinney, 1991), whereas transient separation of infant macaques from their mother results in elevated plasma cortisol concentrations (Levine, Johnson, & Gonzalez, 1985). Furthermore, monkeys raised without maternal contact during the first 6 months of life exhibit increased distress and passive behavior compared to maternally reared peers (Suomi, 1991). In addition, monkeys peer reared during the first 6 months of life also exhibit increased cortisol responses to social situations (Fahlke et al., 2000; Levine, Wiener, & Coe, 1993), a diminished ability to negotiate stressful events (Levine et al., 1993), exaggerated vocalizations (Levine et al., 1993), and increased consumption of alcohol in comparison with maternally reared monkeys (Fahlke et al., 2000; Higley, Hasert, Suomi, & Linnoila, 1991).

Another approach for studying developmental stress in nonhuman primates is the variable foraging demand paradigm. Exposure

of mother-infant dyads of bonnet macaques to varying levels of foraging requirements over a 3-month period results in substantial behavioral dysregulation in infant macaques. In this paradigm, three groups of macaques were utilized: a low foraging demand (LFD) group that was able to easily obtain food, a high foraging demand (HFD) group where acquisition of food was contingent on completion of a daily task, and a variable foraging demand (VFD) group where availability of food was unpredictable. The general rationale of this protocol is that the lack of predictability in food availability within the VFD group leads to maternal distress that is reflected in compromised infant care. Compared to LFD- and HFD-reared macaques, VFD-reared macaques demonstrate anxious temperament and chronically elevated concentrations of CSF CRF in adulthood (Coplan et al., 1996). The elevations in CSF CRF following rearing in the VFD condition are quite stable and still present when measured in adult macaques (Coplan et al., 2001). Furthermore, VFD-reared macaques also exhibit a host of persistent noradrenergic and serotonergic abnormalities (Coplan et al., 2000; Rosenblum et al., 1994). The effects of VFD are not limited to the HPA axis and behavior but VFD also affects other organ systems. Two years after the end of the VFD paradigm, a moderate stressor not only induced a greater cortisol response but also pronounced an immune response as compared to normally reared bonnet macaques of the same age (Smith, Batuman, Trost, Coplan, & Rosenblum, 2002). VFD also produces a greater body weight, higher body mass index (BMI), greater abdominal circumference, and insulin resistance (pre-diabetes) in adult animals than those raised in standard rearing environments (Kaufman et al., 2007).

Collectively, the data derived from rodent and nonhuman primate studies demonstrate that the effects of ELS continue into adulthood in the form of hyperresponsiveness of the HPA axis to environmental stress and abnormal behavior. However, significant limitations exist with respect to the extent that the findings derived from preclinical research in animals may be applied to humans. Aside from the problem of generalization imposed by species differences in brain development and anatomy, much of the present animal literature models reduced, rendered inconsistent, or entirely eliminated interaction between parent and offspring during development, but they do not model physical, sexual, or emotional abuse. These experimental deprivation paradigms appear to be stressful because they subtract care from the social environment during development. Consequently, they are more likely informative of the effects of ''deficit states'' such as neglect, instability of living environment, or parental loss on human stress biology and behavior and thus complement the extensive clinical literature on the consequences of child neglect.

Recently, evidence has come to light to demonstrate the effects of abuse during early life on the HPA axis and behavior in an animal model. Variation in parenting style occurs naturally in rhesus monkeys with differing rates of rejection as characterized by the extent to which the mother limits the timing and duration of contact, suckling, and carrying. Two-year-old female monkeys with a history of higher rates of rejection in the first 6 months of life engaged in more solitary play and higher rates of scratching behavior—a behavior that is indicative of anxiety. Furthermore, offspring with higher rates of rejection had lower CSF 5-hydroxyindoleacetic acid (5-HIAA) concentrations, a major serotonin metabolite, which negatively correlated with the degree of anxiety-like behavior (Maestripieri et al., 2006). Abused infants exhibited delayed independence from their mothers, which included higher rates of distress calls and anxiety as well as differences in play. HPA axis activity was also altered following this naturally occurring abuse. During the first month of life, when abuse is most prevalent, infants had elevated plasma cortisol levels when compared to nonabused infants. However, by 6 months of age, the monkeys exhibited blunted basal cortisol levels and an attenuated ACTH response to CRF compared to control monkeys (McCormack, Sanchez, Bardi, & Maestripieri, 2006). These data demonstrate the effects of abuse early in life on the HPA axis and behavior in an animal model that replicates many of the findings in clinical studies.

PUBERTY—A WINDOW OF INCREASED SUSCEPTIBILITY

The effects of stress during puberty are not as widely studied as those earlier in life; however, this appears to be an additional critical period. If the first episode of an affective disorder manifests during puberty, the individual is much more likely to experience additional episodes later in life when compared to those in which the first episode occurs after 20 years (Weissman, Wolk, Goldstein, et al., 1999; Weissman, Wolk, Wickramaratne, et al., 1999). In addition, bullying is a risk factor for MDD and suicidality in adolescents (Klomek, Marrocco, Kleinman, Schonfeld, & Gould, 2007). The stress-sensitive critical period of puberty may be a particularly important area of study to understand the long-term effects of violence and abuse against women. Data available to date as well as the findings from other critical periods indicate that the HPA axis may be involved in this phenomenon as well. Rodent models also indicated enhanced stress susceptibility during puberty, suggesting that it is a physiological and not psychological phenomenon. Social stress exposure during puberty alters the formation of agonistic behaviors in female golden hamsters (Taravosh-Lahn & Delville, 2004). In addition, social stress during puberty can alter subsequent stress responses (McCormick & Mathews, 2007) as well as substance abuse behaviors in animals (Ferris & Brewer, 1996; McCormick, Robarts, Gleason, & Kelsey, 2004). Exposure to chronic variable stress during puberty enhances the acoustic startle response both at the end of puberty and in adulthood (Maslova, Bulygina, & Popova, 2002). Furthermore, short-term exposure (3 days) to a psychogenic stressor (predator odor and elevated platform) during puberty produces sustained changes in fear-related behavior (Toledo-Rodriguez & Sandi, 2007).

Our understanding of the effects of stress during puberty, a time of profound neurobiological and reproductive changes on mental and physical health is underdeveloped. Of the paucity of data currently available, little of the work has been conducted on female participants. Given the role of estrogen in modulation of the neurobiological response to stress (McEwen, 2002) and the increased risk of violence and abuse exposure for women during this period, it is imperative that research efforts in this area intensify.

GENETIC INFLUENCES ON OUTCOME FROM TRAUMA

Exposure to violence and trauma alone, regardless of stage of development, does not produce adverse effects in all exposed women, and the risk of development of PTSD and depression is, in part, clearly heritable (Bradley et al., 2008; Kaufman et al., 2006; Sullivan, Neale, & Kendler, 2000). Within the field of psychiatric genetics, a major goal of research is to understand how genetic variation alone and in concert with the environment influences individual vulnerability to disease (Figure 2). With respect to stress-related psychiatric illnesses, such as depression and PTSD, a great deal of this work has focused on the identification of candidate genes whose allelic variants are thought to contribute to the risk of disease in the presence of ELS.

The serotonin transporter (*SERT*) gene (Lesch et al., 1993) has repeatedly been implicated as an important candidate gene in association studies conducted with depressed patients. A common functional polymorphism in the 5^0 promoter region of *SLC6A4*, referred to as the 5-HT transporter gene-linked polymorphic region (5-HTTLPR), has been associated with different basal activity of the transporter, most likely related to differential transcriptional activity (Gelernter, Cubells, Kidd, Pakstis, & Kidd, 1999). In a seminal study, Caspi and colleagues (Caspi et al., 2003) used a large and extensively characterized New Zealand cohort to demonstrate that exposure to stress in childhood, in concert with a particular 5-HTTLPR genotype, was predictive of depressive symptoms in adulthood. These results have been widely replicated (Cervilla et al., 2007; Lenze et al., 2005; Nakatani et al., 2005; Zalsman et al., 2006;). Building on these initial findings, Kaufman and colleagues reported that particular variants of the *SERT* gene and the Met allele of the brain-derived neurotrophic factor (BDNF), a neurotrophin linked to neuronal pathology and responsive to antidepressants, Val66Met polymorphism in the

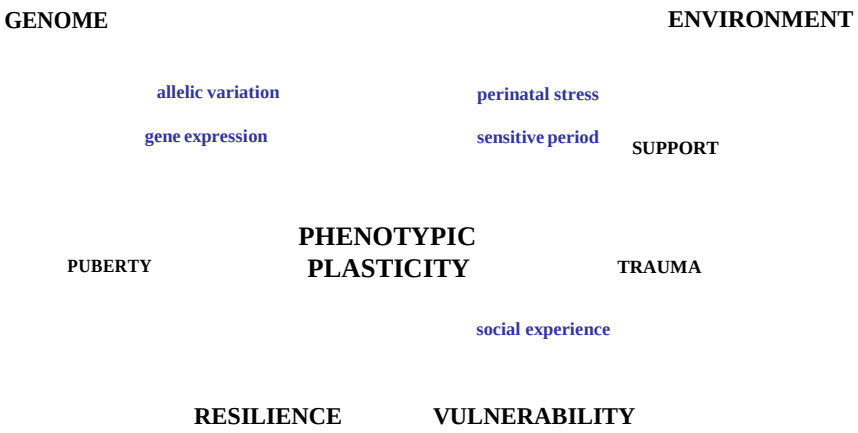

FIGURE 2: The manifestation of psychiatric diseases such as MDD and PTSD is modulated by the interactions of genetics and the environment. Some gene x environment interactions confer resilience while others produce vulnerability. Development is a time of particular susceptibility to negative gene x environment interactions leading to increased risk for manifestation of psychiatric and somatic disorders when exposed to negative environmental conditions prior to the end of adolescence. Epigenetic changes in response to stress exposure are not limited to the exposed individual but are transmitted between generations perpetuating the adverse effects.

presence of ELS, influence the development of depression in children (Kaufman et al., 2006). Similar findings, in terms of the effects of stressful life events on depression risk as a function of SERT and Val66Met genotype, have also been reported in a geriatric Korean cohort (Kim et al., 2007). BDNF may influence the risk of depression by altering reactivity of the HPA axis. Homozygous carriers of the Met/Met genotype demonstrate significantly higher HPA axis activity during the dexamethasone/CRF test than patients carrying the Val/Val or Val/Met genotype (Schule et al.,2006).

Allelic variants within genes coding for elements of the HPA axis that influence the risk of depression and PTSD in individuals with a history of ELS have recently been identified. Data from a large sample of heavily traumatized, inner-city African Americans identify single nucleotide polymorphisms (SNPs) as well as haplotypes within the *CRHR1* gene that predict scores on the Beck Depression Inventory as a function of trauma exposure (Bradley et al., 2008). Using an overlapping sample, SNPs of the *FKBP5* gene, which codes for a key regulator of the glucocorticoid receptor, were found to interact with child abuse severity to predict PTSD symptoms in adults (Binder et al., 2008).

For those individuals exposed to early life trauma, both gene gene and gene environment interactions likely influence the development of depression and other disorders. Notably, the genetic variants described by several studies only confer the risk of depression and PTSD in the setting of childhood maltreatment. These data highlight the critical role of developmental timing and environmental influences on the expression of genetic risk of psychiatric illness. Continued efforts to elucidate the genetic variables that confer risk and resilience on individuals exposed to stress during development may enhance our ability to protect and more effectively treat young women and to identify ''at-risk'' populations.

PLEIOTROPIC EFFECTS OF ELS

The research described thus far in this review demonstrates that trauma exposure and neglect during early life as well as in adulthood substantially elevate adult risk of mood and

anxiety disorders (Chapman et al., 2004; Dube et al., 2001; Felitti et al., 1998; Gladstone et al., 2004; McCauley et al., 1997) and alter HPA axis physiology (Heim et al., 2000; Heim & Nemeroff, 2001; Heim et al., 2001). However, the detrimental effects of early life abuse and trauma are not limited to mental health and stress physiology. Trauma exposure early in life has also been linked to both substance abuse (Felitti et al., 1998; McCauley et al., 1997) and unintended first pregnancy (Dietz et al., 1999). Furthermore, the implications of early life trauma reach beyond mental health and behavior and have remarkable implications for somatic health. ELS exposure increases the incidence of systemic inflammation (Danese, Pariante, Caspi, Taylor, & Poulton, 2007; Danese et al., 2008) and a variety of medical illnesses, including obesity (Felitti et al., 1998; Gunstad et al., 2006; Lissau & Sorensen, 1994), cardiovascular disease (Batten, Aslan, Maciejewski, & Mazure, 2004; Caspi, Harrington, Moffitt, Milne, & Poulton, 2006; Dong et al., 2004; Goodwin & Stein, 2004), cerebrovascular disease (Smith, Hart, Blane, & Hole, 1998), diabetes mellitus (Goodwin & Davidson, 2005; Goodwin & Stein, 2004;), cancer (Smith et al., 1998), and autoimmune disorders (Goodwin & Stein, 2004). Furthermore, a graded relationship appears to exist between exposure to trauma and psychiatric/health morbidity in adulthood (Felitti et al., 1998; McCauley et al., 1997). Although the biology of the interrelationships among ELS, mental illness, and somatic illness are just beginning to be understood, the lifelong effects of ELS on both mental and physical health are well documented and the HPA axis is a likely mediator of both types of pathophysiology.

PTSD in particular, and certain forms of mood and anxiety disorders in general, have been associated with dysregulation of the nervous (Armony, Corbo, Clement, & Brunet, 2005; Forbes, Miller, Cohn, Fox, & Kovacs, 2005; Guthrie & Bryant, 2005; Hendler et al., 2003; Orr et al., 2003; Orr, Lasko, Shalev, & Pitman, 1995; Rauch et al., 2000; Wessa, Karl, & Flor, 2005), neuroendocrine (Carpenter et al., 2004; Heim et al., 2000; Yehuda et al., 1993, 1995, 2001; Yehuda, Golier, & Kaufman, 2005), and immune systems (Miller, Stetler, Carney, Freedland, & Banks, 2002; Pace et al., 2006). Of note, each of these systems is involved directly in the acute adaptation to stress. One hypothesis for the etiology of PTSD and other forms of psychopathology is that exposure to stressful events results in a constellation of persisting organ-specific pathophysiology that affects susceptibility to psychiatric illness. The developmental timing of exposure to such events is clearly important because considerable data have demonstrated that exposure to stressful events during childhood is associated with the presence of altered functioning in adults of the cardiovascular (Luecken, 1998), neuroendocrine (Heim et al., 2000; Luecken, 1998, 2001), and immune systems (Pace et al., 2006). These alterations may cumulatively contribute to the etiology, maintenance, and progression of various forms of trauma-related psychiatric and medical illness through persisting activation of these stress-responsive organ systems.

MULTIGENERATIONAL EFFECTS OF VIOLENCE AND TRAUMA

The potential for generational effects of abuse against women has already been alluded to in this review, but given the profound implications of abuse toward women on subsequent generations, we felt it was warranted to directly address this issue. There are several avenues by which abuse can reverberate among generations, which include adverse effects on the fetus during pregnancy, effects on maternal behavior, and epigenetic effects.

Pregnancy and Stress

Epidemiological data indicate that up to 20% of pregnant women experience one or more episodes of abuse during pregnancy (Shoffner, 2008). In addition, we have already established that women with a history of abuse, particularly early in life, are at higher risk of depression and anxiety disorders. Recent work indicates that maternal depression may itself represent the first adverse life event to which one can be exposed. The relationship between maternal depression and infant salivary cortisol concentrations was examined in 6-month-old infants. Maternal history of depression was

associated with elevated baseline infant cortisol concentrations and active peripartum depression was associated with higher infant cortisol secretion in response to brief restraint stress. These data suggest that exposure to a depressed mother either in utero or in the first months of life may alter the HPA axis (Brennan et al., 2008). Additional clinical evidence for maternal state effects on the unborn child stems from the September 11, 2001 attacks in New York City. At 9 months of age, infants born to mothers who developed PTSD following exposure to the September 11 had lower salivary cortisol than infants born to unexposed individuals. This effect was most pronounced in infants whose mothers were in the third trimester of pregnancy at the time of the attacks (Yehuda, Engel, et al., 2005).

Our understanding of the maternal state on the physical well-being of the offspring has been greatly advanced by preclinical work with animal models. Carefully controlled studies have clearly established that exposing the mother to a stressful or abusive environment is akin to exposing the fetus directly. Given that stress exposure in the laboratory animal studies is mild compared with the magnitude of stress and trauma experienced by women afflicted by violence and abuse, the demonstrable physiological repercussions for the offspring after maternal stress exposure are remarkable. Case in point, exposure of a pregnant guinea pig to a strobe light, an aversive but not physically harmful stimulus, during late gestation results in sustained HPA axis abnormalities, disruption of the sex steroid systems, and increased anxiety-like behavior in the offspring. Two hours of light stress on 3 consecutive days of gestation caused persistent changes in the pups. The offspring of guinea pigs exposed to these aversive conditions exhibited elevations in basal and stress-induced corticosterone concentrations, suggesting abnormalities in both basal and stress-induced function of the HPA axis. Furthermore, exposure to stress during gestation caused an increase in anxiety-like behavior, as demonstrated by increased wall-seeking behavior in adult offspring (Kapoor & Matthews, 2005).

The noxious effects of seemingly innocuous stressors are not unique to guinea pigs, specifically, or rodents in general. Primates exhibit similar responses to aversive, although innocuous, stimuli. In addition, the effects in primates extend beyond the HPA axis to multiple organ systems. Acoustic stress for 10 min a day during 30% of gestation of rhesus monkeys resulted in multiple physiological and behavioral alterations, including HPA axis changes. Although overt somatic growth was unchanged, this relatively mild stressor caused immature neuromotor reflexes in the neonate and increased emotional reactivity. A modified Brazelton Newborn Behavioral Assessment Scale was used to assess the neuromotor reflexes of the neonate rhesus monkeys. Infants derived from stressed pregnancies showed early impairments in motor coordination and muscle tone and shorter attention spans when compared to controls (Schneider, 1992; Schneider, Coe, & Lubach, 1992). This mild stressor also altered immune function including abnormal lymphocyte responses to cytokines and hormones (Coe, Kramer, Kirschbaum, Netter, & Fuchs, 2002) and altered bacterial colonization of the gut of infant monkeys (Bailey, Lubach, & Coe, 2004). CNS abnormalities were also evident in young adult offspring after maternal exposure to acoustic stress as evidenced by smaller corpus callosal size (Coe, Lulbach, & Schneider, 2002) and hippocampal pathology. Monkeys whose mothers were exposed to acoustic stress during gestation had reduced hippocampal volume, inhibition of neurogenesis in the dentate gyrus, increased HPA axis reactivity, and a behavioral profile consistent with increased emotional reactivity at 2–3 years of age (Coe et al., 2003). Collectively, these data demonstrate the profound effects of prenatal stress exposure. The reported changes in brain morphology are consistent with changes found following severe forms of chronic stress in rodents (McEwen & Magarinos, 2001) or after trauma in humans (Yehuda, Golier, et al., 2005). These findings are particularly disturbing because the mothers in these studies were exposed to what is roughly equivalent to a loud noise and their offspring were profoundly affected. These preclinical data highlight the clinical potential for even verbal and psychological abuse during pregnancy to alter the brain and behavior of the unborn child.

Multiple hormones and neurotransmitters change in response to a stressor, but laboratory findings suggest a particularly salient role for glucocorticoids in the production of the lifelong effects of exposure to gestational stress. The administration of dexamethasone, a synthetic glucocorticoid, exerts similar effects on the fetus as prenatal stress. When administered during the last week of gestation, dexamethasone alters the development of the HPA axis. Thus, corticosterone concentrations are higher in dexamethasone-exposed offspring than in saline-treated controls (Levitt, Lindsay, Holmes, & Seckl, 1996; Welberg, Seckl, & Holmes et al., 2001). Glucocorticoid exposure in utero can retard brain weight and delay maturation of neurons, myelination, glia, and vasculature (Huang, Harper, Evans, Newnham, & Dunlop, 2001a, 2001b). In addition, in utero exposure to glucocorticoids alters neuronal structure and synapse formation (Antonow-Schlorke, Schwab, Li, & Nathanielsz, 2003) and may permanently alter brain structure (Matthews, 2000). Furthermore, glucocorticoid exposure increases CRF concentrations in the amygdala and fear and anxiety-like behaviors (Welberg, Seckl, & Holmes, 2000; Welberg et al., 2001).

In addition to neuronal consequences of excess glucocorticoid exposure, adverse effects on the cardiovascular system have been reported. Prenatal exposure to glucocorticoids alters the vascular response to vasoconstrictors and attenuates vasorelaxation in sheep, suggestive of microvascular dysfunction (Docherty et al., 2001; Molnar, Nijland, Howe, & Nathanielsz, 2002). Rats exposed to prenatal stress demonstrate longer lasting hypertension following restraint stress in adulthood than control rats (Igosheva, Klimova, Anishchenko, & Glover, 2004). Prenatally stressed rats also exhibit prolonged heart rate responses to acute stress and delayed recovery when compared to controls, and these effects are more pronounced in females than in males (Igosheva et al., 2004). In humans, changes of this nature in the cardiovascular system can increase the risk and severity of cardiovascular disease later in life (McMillen et al., 2008).

Collectively, these data demonstrate that prenatal stress can produce long-term effects on the HPA axis as well as on major organ systems in the offspring. The preclinical data available to date suggest a preeminent role for glucocorticoids in these effects. Women who are victims of abuse represent a particularly ''at-risk'' population of mothers because their unborn children are exposed to the mental and physiological repercussions of the mother's early life trauma as well as the mental and physiological effects of current abuse.

Maternal Behavior and Epigenetics

The effects of trauma cross the generational boundary and significantly alter the mental health of the subsequent generation. Some of these effects are likely due to epigenetic changes in the DNA (Meaney, Szyf, & Seckl, 2007), but there is also a strong environmental effect of being raised by an abused parent. Environmental effects are illustrated by the finding that children of Holocaust survivors with PTSD report more neglect and emotional abuse than demographically comparable children of parents without PTSD (Yehuda et al., 2000). Regardless of epigenetic or environmental origins, adult children of Holocaust survivors exhibit an increased incidence of mood disorders and multiple alterations in HPA axis function. Adult children of Holocaust survivors have a greater lifetime prevalence of PTSD, as well as other mood and anxiety disorders, than demographically similar persons with a similar lifetime trauma exposure (Yehuda, Schmeidler, Giller, Siever, & Binder-Brynes, 1998). The children of Holocaust survivors who were exposed to trauma but did not manifest PTSD were also at an increased risk of mental health disorders when compared to individuals with unexposed parents (Yehuda, Halligan, & Bierer, 2001).

As mentioned, one potential mechanism for the increased prevalence of mood and anxiety disorders is altered HPA axis physiology. Children of Holocaust survivors have significantly lower 24-h urinary cortisol secretion when

compared with control participants, and offspring of holocaust-surviving parents with PTSD had lower cortisol levels than offspring of Holocaust survivors that did not manifest PTSD (Yehuda et al., 2000). In addition, adult children of Holocaust survivors who manifested PTSD exhibit enhanced cortisol negative feedback inhibition in response to a dexamethasone suppression test (DST; Yehuda, Blair, Labinsky, & Bierer, 2007). Collectively, these data demonstrate that abuse can alter HPA axis activity and risk of psychiatric disorder at least one generation removed from the trauma exposure.

Preclinical studies also demonstrate the impact of altered maternal care on the offspring. The effects of maternal separation during development on the stress response of rodents have been studied in depth (Ladd et al., 2000). Adult rats repeatedly separated as pups from dams for variable amounts of time exhibit enhanced activity and dysregulation of the HPA axis (Ladd, Huot, Thrivikraman, Nemeroff, & Plotsky, 2004; Ladd, Owens, & Nemeroff, 1996; Ladd, Thrivikraman, Huot, & Plotsky, 2005; Plotsky & Meaney, 1993), increased CRF mRNA expression within areas of the brain that facilitate adaptation to stress or threat (Ladd et al., 2005; Plotsky & Meaney, 1993), increased frequency of anxious behavior (Huot, Thrivikraman, Meaney, & Plotsky, 2001; Ladd et al., 2005), and increased ethanol preference (Huot et al., 2001). The adverse consequences of early maternal separation are reversed by treatment with antidepressants (Huot et al., 2001) and prevented by provision of an enriched environment (Francis, Diorio, Plotsky, & Meaney, 2002) or surrogate maternal care during development (Huot, Gonzalez, Ladd, Thrivikraman, & Plotsky, 2004).

Studies of natural variations in maternal behavior of rodents also demonstrate profound effects on the HPA axis and behavior. Meaney and colleagues have extensively studied the differences in offspring of rats which engage in high and low levels of maternal care (Fish et al., 2004; Meaney & Szyf, 2005; Szyf, Weaver, & Meaney, 2007; Zhang, Parent, Weaver, & Meaney, 2004). These studies have linked the differences in HPA axis responsiveness to an epigenetic change that is catalyzed by the varying levels of maternal care. Specifically, altered histone acetylation and transcription factor (*NGFI-A*) binding to the glucocorticoid receptor promoter differs between the progeny of different care types. The increases in NGFI-A induced by higher levels of maternal care are hypothesized to increase transcription and thereby increase glucocorticoid receptor mRNA (Szyf et al., 2005). Recently, a similar epigenetic effect has been reported in the clinical population. Analysis of genomic DNA from mononuclear cells of cord blood of term fetuses demonstrated that higher levels of reported maternal stress during the third trimester were associated with more methylation at the NGFI-A-binding site. These increases in methylation were also associated with higher salivary cortisol stress responses at 3 months of age (Oberlander et al., 2008).

Additional work is necessary to elucidate the mechanisms by which HPA axis stress-induced changes and the mental and physical consequences of these changes pass between generations. However, it is undeniable that the effects of abuse are not limited to the immediate victims. The mental and physical consequences of abuse reverberate through generations.

TREATMENT IMPLICATIONS OF ELS EXPOSURE

The data described in this review indicate that patients with depression or PTSD and a history of ELS, such as physical and sexual abuse, may constitute unique endophenotypes with respect to treatment response and course of illness. Such patients may require a unique treatment protocol. ELS has been found to impact the clinical response of depressed patients to pharmacotherapy (Hayden & Klein, 2001; Kaplan & Klinetob, 2000), and the presence or absence of ELS in patients with chronic depression appears to moderate their response to pharmacotherapy, psychotherapy, or a combination of both (Nemeroff et al., 2003). Furthermore, patients with depression and a

history of ELS have been reported to exhibit increased rates of relapse following successful treatment of depression (Lara, Klein, & Kasch, 2000). These data highlight the importance of a strong therapeutic alliance in the treatment of chronic depression. Chronicity is a more common feature of depression in those with a history of ELS than for individuals with depression without a history of childhood neglect or abuse. Breaking the cycle of abuse may also break the pattern of chronic and relapsing depression.

ELS AND MODIFYING FACTORS

Preclinical and clinical research examining the psychobiology of stress and trauma exposure, with a primary emphasis on the pathophysiological response of vulnerable individuals, has generated growing interest in the reciprocal research area of resilience factors that mitigate the negative effects of stress and trauma exposure (Bonanno & Mancini, 2008). Preclinical work in rodents has demonstrated that environmental enrichment during puberty can mitigate some of the anxiety-related effects of ELS (Imanaka, Morinobu, Toki, & Yamawaki, 2006; Imanaka et al., 2008). The restorative effects of environmental enrichment are in part facilitated by changes in gene expression of glutamate receptor subunits (Bredy, Zhang, Grant, Diorio, & Meaney, 2004). An additional mechanism of modification of ELS effects, that has proven effective in the laboratory, is pharmacological induction of epigenetic changes through alterations of DNA methylation and histone modification (Weaver, Meaney, & Szyf, 2006). In general, research into resilience factors in humans consisted predominantly of descriptive research examining the psychological (Bonanno & Mancini, 2008; Haglund, Nestadt, Cooper, Southwick, & Charney, 2007; Mancini & Bonanno, 2006) and biological (Haglund et al., 2007; Ozbay, Fitterling, Charney, & Southwick, 2008) characteristics of resilient individuals. Research focused on the psychological characteristics of resilient individuals has resulted in the development of provisional clinical strategies to enhance the adaptation of vulnerable individuals to acute and/or chronic exposure to traumatic or nontraumatic stressful experience (Mancini & Bonanno, 2006).

SUMMARY AND CONCLUSIONS

Conservative estimates suggest that each year in the United States more than 1,000,000 children are exposed to sexual or physical abuse or neglect (Sedlack & Broadhurst, 1996). The research summarized in this chapter clearly demonstrates that exposure to stress prior to adulthood can result in persistent effects on both mental and physical health. Even prior to birth, children are particularly sensitive to the effects of stress, and this sensitivity continues after birth through puberty. Exposure to violence and abuse can alter the function of the HPA axis throughout one's life, and these changes are accompanied by increased incidence and severity of MDD, PTSD, and other anxiety disorders, somatic diseases such as cardiovascular disease, and perhaps cancer and diabetes. Reducing the exposure of women to violence and abuse would reduce the risk and severity of multiple mental and physical illnesses and stop the transgenerational cycle of abuse-related pathology. In addition, a better understanding of the mechanisms that underlie the pervasive effects of early life abuse will lead to additional behavioral and pharmacological treatment strategies.

IMPLICATIONS FOR PRACTICE, POLICY, AND RESEARCH

- Practice: Successful treatment of mental and physical disorders in survivors of early life abuse and trauma may be distinct from treatment of unexposed individuals.
- Policy: Given that abuse against women impacts the immediate victim as well as subsequent generations, and there are no cures for the lasting effects of the abuse, prevention of abuse is the single best course of action.
- Research: Additional basic and clinical research on biological mechanisms of abuse-induced changes in the HPA axis of women will ultimately improve treatment.

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SUGGESTED READINGS

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